(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 June 2008 (26.06.2008)

PCT

(10) International Publication Number
WO 2008/077110 A2

(51) International Patent Classification:
A61L 12/14 (2006.01) *C11D 7/26* (2006.01)
A01N 47/44 (2006.01) *A61K 9/00* (2006.01)
A01N 33/12 (2006.01) *A61L 101/34* (2006.01)
C11D 3/22 (2006.01) *A61L 101/44* (2006.01)
C11D 3/37 (2006.01) *A61L 101/46* (2006.01)

(21) International Application Number:
PCT/US2007/088167

(22) International Filing Date:
19 December 2007 (19.12.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
11/613,029 19 December 2006 (19.12.2006) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

WO 2008/077110 A2

(54) Title: IMPROVED OPHTHALMIC AND CONTACT LENS SOLUTIONS CONTAINING SIMPLE SACCHARIDES AS PRESERVATIVE ENHANCERS

(57) Abstract: The present invention relates to ophthalmic solutions comprising 0.00001 up to 0.001 weight percent of a simple saccharide, at least 0.00001 weight percent of a preservative, and not more than about 0.2 percent by weight chloride. The simple saccharide is chosen from the group consisting of: inositol; mannitol; sorbitol; sucrose; dextrose; glycerin; propylene glycol; ribose; triose; tetrose; erythrose; threose; pentose; arabinose; ribulose; xylose; xylulose; lyxose; hexose; allose; altrose; fructose; galactose; glucose; gulose; idose; mannose; sorbose; talose; tagatose; adlose; ketose; heptose; sedoheptulose; monosaccharides; disaccharides; sugar alcohols; xylitol; and polyol.

IMPROVED OPHTHALMIC AND CONTACT LENS SOLUTIONS CONTAINING SIMPLE SACCHARIDES AS PRESERVATIVE ENHANCERS

Cross-Reference to Related Applications

[0001] This application claims the benefit of U.S. Patent Application Serial No. 11/613,029, filed December 19, 2006.

Field of the Invention

[0002] The present invention relates to the field of ophthalmic solutions and their uses. In particular the invention relates to contact lens cleaning solutions, contact lens rinsing and storing solutions, solutions to deliver active pharmaceutical agents to the eye, solutions for disinfecting ophthalmic devices and the like.

Background

[0003] The present invention relates to the field of ophthalmic solutions and especially to the aspects of preservative efficacy and comfort after prolonged use. These ophthalmic solutions have been used for some period of time and are available as over the counter products. Solutions that are used in direct contact with corneal tissue such as the delivery of active pharmaceutical agent to the eye, or indirectly, such as the cleaning, conditioning or storage of devices that will come in contact with corneal tissue, such as contact lenses, there is a need to insure that these solution do not introduce sources of bacterial or other microbial infection. Thus preservatives are included to reduce the viability of microbes in the solution and to lessen the chance of contamination of the solution by the user since many of the solutions are bought, opened, used, sealed and then reused.

[0004] State of the art preservative agents include polyhexamethylene biguanide (PHMB), Polyquad ™, chlorhexidine and benzalkonium chloride, and the like, all of which at some concentration irritate corneal tissue and lead to user discomfort. Therefore, a solution that employs a given amount of a preservative agent, but which is made more effective by addition of an agent that is not a preservative agent would be desired.

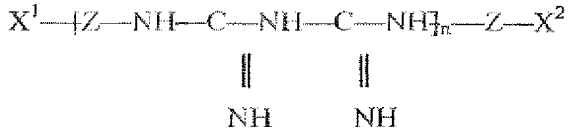
Summary of the Invention

[0005] The present invention relates to improved ophthalmic solutions that employ inositol and other simple saccharides in order to more effectively preserve solutions and to reduce the degree to which cationic preservatives will deposit on contact lenses. Ophthalmic solutions are here understood to include contact lens treatment solutions, such as cleaners, soaking solutions, conditioning solutions and lens storage solutions, as well as wetting solutions and in-eye solutions for treatment of eye conditions.

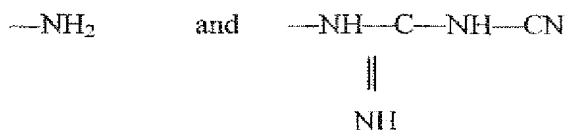
[0006] More specifically, the invention relates to an ophthalmic solution comprising 0.00001 to 10.0 weight percent of a simple saccharide, at least 0.00001 weight percent of a preservative, and not more than about 0.2 percent by weight chloride. The simple saccharide may be chosen from the group consisting of: inositol; mannitol; sorbitol; sucrose; dextrose; glycerin; propylene glycol; ribose; triose; tetrose; erythrose; threose; pentose; arabinose; ribulose; xylose; xylulose; lyxose; hexose; allose; altrose; fructose; galactose; glucose; gulose; idose; mannose; sorbose; talose; tagatose; adlose; ketose; heptose; sedoheptulose; monosaccharides; disaccharides; sugar alcohols; xylitol; and polyol.

[0007] The solutions specifically described herein have 0.00001 to about 10.0 percent of simple saccharides in combination with other active ingredients useful in ophthalmic solutions such as buffers, preservatives, surfactants, and antimicrobial agents, and with a low chloride concentration, not more than about 0.2 percent by weight. It has been found, surprisingly that inositol, and other sugars including mannitol, sorbitol, sucrose, dextrose, glycerin and propylene glycol, effectively increase the antibacterial effect of preservatives in low salt (low chloride) conditions.

[0008] The preservatives that are specifically useful are include polyhexamethylene biguanide (PHMB), Polyquad ™, chlorhexidne, and benzalkonium chloride, as well as other cationic preservatives that may prove useful in the present invention as well. The cationic preservatives are used at effective amounts as preservatives, and in the instance of PHMB from 0.0001 percent by weight to higher levels of about 0.01 weight percent. Specifically, The cationic polymeric preservative includes polymeric biguanides such as polymeric hexamethylene biguanides (PHMB), and combinations thereof. Such cationic polymeric biguanides, and water-soluble salts thereof, having the following formula:



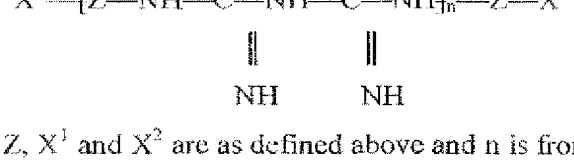
[0009] wherein Z is an organic divalent bridging group which may be the same or different throughout the polymer, n is on average at least 3, preferably on average 5 to 20, and X^1 and X^2 are



[0010] One preferred group of water-soluble polymeric biguanides will have number average molecular weights of at least 1,000 and more preferably will have number average molecular weights from 1,000 to 50,000. Suitable water-soluble salts of the free bases include, but are not limited to hydrochloride, borate, acetate, gluconate, sulfonate, tartrate and citrate salts.

[0011] The above-disclosed biguanides and methods of preparation are described in the literature. For example, U.S. Pat. No. 3,428,576 describes the preparation of polymeric biguanides from a diamine and salts thereof and a diamine salt of dicyanimide.

[0012] Most preferred are the polymeric hexamethylene biguanides, commercially available, for example, as the hydrochloride salt from Avecia (Wilmington, Del.) under the trademark Cosmocil™ CQ. Such polymers and water-soluble salts are referred to as polyhexamethylene (PHMB) or polyaminopropyl biguanide (PAPB). The term polyhexamethylene biguanide, as used herein, is meant to encompass one or more biguanides have the following formula:



[0013] wherein Z, X^1 and X^2 are as defined above and n is from 1 to 500.

[0014] Depending on the manner in which the biguanides are prepared, the

predominant compound falling within the above formula may have different X^1 and X^2 groups or the same groups, with lesser amounts of other compounds within the formula. Such compounds are known and are disclosed in U.S. Pat. No. 4,758,595 and British Patent 1,432,345, which patents are hereby incorporated. Preferably, the water-soluble salts are compounds where n has an average value of 2 to 15, most preferably 3 to 12.

[0015] It was found that an unexpected preservative efficacy was displayed when inositol was used in conjunction with the cationic preservative. The other components of the solution are used at levels known to those skilled in the art in order to improve the wearability of lenses and when used directly in the eye, to provide increased resistance to infection. Inositol used in ophthalmic solutions increases preservative efficacy in certain formulations, provides increased resistance to infection in corneal tissue, in certain formulations, and improves the quality of tears in certain formulations.

[0016] The formulations may also include buffers such as phosphate, bicarbonate, citrate, borate, ACES, acetate, BES, BICINE, BIS, BIS-Tris, BIS-Tris Propane, bicarbonate, histidine, HEPES, Tris, HEPPS, imidazole, MES, MOPS, PIPES, TAPS, TES, glycine, tiomethamine, and Tricine.

[0017] Surfactants that might be employed include polysorbate surfactants, polyoxyethylene surfactants, phosphonates, saponins and polyethoxylated castor oils, but preferably the polyethoxylated castor oils. These surfactants are commercially available. The polyethoxylated castor oils are sold by BASF under the trademark Cremaphor.

[0018] Inositol, mannitol, sorbitol, sucrose, dextrose, glycerin, propylene glycol and the other agents used in the present invention are all commercially available, and well enough understood to be formulated into products within the scope of the invention by those skilled in the art.

[0019] The solutions of the present invention may contain other additives including but not limited to buffers, tonicity agents, demulcents, wetting agents, preservatives, sequestering agents (chelating agents), surface active agents, and enzymes.

[0020] Other aspects include adding to the solution from 0.001 to 1 weight percent

chelating agent (preferably disodium EDTA) and/or additional microbicide, (preferably 0.00001 to 0.1 or 0.0000 1 to 0.01) weight percent polyhexamethylene biquanide (PHMB, N-alkyl-2-pyrrolidone, chlorhexidine, polyquaternium- 1, hexetidine, bronopol, alexidine, low concentrations of hydrogen peroxide, and ophthalmologically acceptable salts thereof.

[0021] Ophthalmologically acceptable chelating agents useful in the present invention include amino carboxylic acid compounds or water-soluble salts thereof, including ethylenediaminetetraacetic acid, nitrilotriacetic acid, diethylenetriamine pentaacetic acid, hyd roxyethylethylenediaminetriacetic acid, 1 ,2-diaminocyclohexanetetraacetic acid, ethylene glycol bis (beta-aminoethyl ether) in N, N, N', N' tetraacetic acid (EGTA), aminodiacetic acid and hydroxyethylamino diacetic acid. These acids can be used in the form of their water soluble salts, particularly their alkali metal salts. Especially preferred chelating agents are the di-, tn- and tetra-sodium salts of ethylenediaminetetraacetic acid (EDTA), most preferably disodium EDTA (Disodium Edetate).

[0022] Other chelating agents such as citrates and polyphosphates can also be used in the present invention. The citrates which can be used in the present invention include citric acid and its mono-, di-, and tri-alkaline metal salts. The polyphosphates which can be used include pyrophosphates, triphosphates, tetraphosphates, trimetaphosphates, tetrametaphosphates, as well as more highly condensed phosphates in the form of the neutral or acidic alkali metal salts such as the sodium and potassium salts as well as the ammonium salt.

[0023] The pH of the solutions should be adjusted to be compatible with the eye and the contact lens, such as between 6.0 to 8.0, preferably between 6.8 to 7.8 or between 7.0 to 7.6. Significant deviations from neutral (pH 7.3) will cause changes in the physical parameters (i.e. diameter) in some contact lenses. Low pH (pH less than 5.5) can cause burning and stinging of the eyes, while very low or very high pH (less than 3.0 or greater than 10) can cause ocular damage.

[0024] The additional preservatives employed in the present invention are known, such as polyhexamethylene biguanide, N-alkyl-2-pyrrolidone, chlorhexidine, polyhexamethylenebiguanide, alexidine, polyquaternium- 1, hexetidine, bronopol and a very

low concentration of hydrogen peroxide, e.g., 30 to 200 ppm.

[0025] The solutions of the invention are compatible with both rigid gas permeable and hydrophilic contact lenses during storage, cleaning, wetting, soaking, rinsing and disinfection.

[0026] A typical aqueous solution of the present invention may contain additional ingredients which would not affect the basic and novel characteristics of the active ingredients described earlier, such as tonicity agents, surfactants and viscosity inducing agents, which may aid in either the lens cleaning or in providing lubrication to the eye. Suitable tonicity agents include sodium chloride, potassium chloride, glycerol or mixtures thereof. The tonicity of the solution is typically adjusted to approximately 240 milliosmoles per kilogram solution (mOsm/kg) to render the solution compatible with ocular tissue and with hydrophilic contact lenses. In one embodiment, the solution contains 0.01 to 0.2 weight percent sodium chloride. The important factor is to keep the concentrations of such additives to a degree no greater than that would supply a chloride concentration of no greater than about 0.2 mole percent.

[0027] Suitable viscosity inducing agents can include lecithin or the cellulose derivatives such as hydroxymethylcellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose (HPMC), and methylcellulose in amounts similar to those for surfactants, above.

Example 1

[0028] An example of a formulation containing low salt, a buffer and cationic preservative follows:

Log

Reduction	Buffer	Preservative	Preservative Enhancer	Wetting Agent
2.27	none	PHMB 0.0001%	None	None
3.85	Bis-Tris Propane	PRMB 0.0001%	None	cremophor ®RH

	0.2%			40
4.00	Bis-Tris Propane 0.2%	PHMB 0.0001%	propylene glycol 3%	cremophor ®RH 40
4.40	Bis-Tris Propane 0.2%	PHMB 0.0001%	sorbitol 5%	cremophor®RH 40
4.40	Bis-Tris Propane 0.2%	PHMB 0.0001%	inositol 5%	cremophor ®RH 40
2.98	Marketed Product 1			
0.68	Marketed Product 2			
2.99	Marketed Product 3			

[0029] Column 1 shows the reduction of C. *albicans* at 2 hours using a typical antibacterial test. The data shows improved activity over the preservative alone; improved activity over the buffer control without sugar additive and improved activity over commercially available products

Example 2

Log

Reduction	**Buffer**	**Preservative**	**Additive**
2.53	None	PHMB 0.0001%	none
1.34	Bis-Tris Propane 0.2%	PHMB 0.0001%	sodium chloride 0.5%
3.42	Bis-Tris Propane 0.2%	PHMB 0.0001%	glycerin 0.5%
2.73	Bis-Tris Propane 0.2%	PHMB 0.0001%	propylene glycol 05%
1.13	Bis-Tris Propane 0.2%	PHMB 0.0001%	potassium chloride 0.5%
3.92	Bis-Tris Propane 0.2%	PHMB 0.0001%	sorbitol 0.5%
3.23	Bis-Tris Propane 0.2%	PHMB 0.0001%	mannitol 0.5%
3.06	Bis-Tris Propane 0.2%	PHMB 0.0001%	inositol 0.5%
3.72	Bis-Tris Propane 0.2%	PHMB 0.0001%	dextrose 0.5%

[0030] This data shows that the antimicrobial activity of buffer with the sugar or glycol is greater than the preservative alone and that decreased activity at 0.5% sodium chloride or 0.5% potassium chloride solutions occurs as well. Thus the surprising effect of the sugar derived preservative enhancers is displayed and the effects relationship to chloride concentration is demonstrated.

Example 3

[0031] Solutions with a cationic polymeric preservative (PHMB) sodium chloride and glycerin and a buffer were made as shown in the following table and the preservative efficacy was measured.

Log

Reduction	Buffer	Preservative	Sodium Chloride	Glycerin
1.69	none	PHMB 0.0001%	none	none
1.74	none	PHMB 0.0001%	0.1%	none
1.46	none	PHMB 0.0001%	0.2%	none
0.86	none	PHMB 0.0001%	0.4%	none
0.49	none	PHMB 0.0001%	0.5%	none
2.44	Bis-Tris Propane 0.2%	PHMB 0.0001%	none	none
1.89	Bis-Tris Propane 0.2%	PHMB 0.0001%	0.1%	none
1.54	Bis-Tris Propane 0.2%	PHMB 0.0001%	0.2%	none
0.98	Bis-Tris Propane 0.2%	PHMB 0.0001%	0.4%	none
0.89	Bis-Tris Propane 0.2%	PHMB 0.0001%	0.5%	none
2.46	Bis-Tris Propane 0.2%	PHMB 0.0001%	none	0.20%

2.41	Bis-Tris Propane 0.2%	PHMB 0.0001%	none	0.50%

[0032] The above date illustrates the effect of sodium chloride on preservative efficacy and the effect of glycerin in improving preservative efficacy in low salt solutions.

Example 4

[0033] Solutions were made according to methods described supra with sodium phosphate as the buffer.

Log

Reduction	Buffer	Preservative	Tonicity Agent
0.79	Sodium Phosphate 0.2%	PHMB 0.0001%	none
0.33	Sodium Phosphate 0.2%	PHMB 0.0001%	Sodium Chloride 0.7%

[0034] This data illustrates the problem with sodium chloride is independent of buffer type.

Example 5

[0035] Solutions were formulated with sodium chloride, sorbitol and sucrose and then lenses were immersed in the resultant solutions and chlorohexidine gluconate was added. The lenses were exposed for 3 hours and the amount of the chlorohexidine deposited on the lens was measured.

Method: HPLC analysis for chlorhexidine gluconate

3.0 mL solution exposed to 1/2 lens

Matrix: 1 ppm CHG /0.2% Bis-Tris Propane /0.1% Cremophor RH 40

Lens: Freshlook ColorBlends (45% phemfilcon A, 55% water) Wesley Jess

Additive	ug CHG per lens	% Decrease
None	4.0	67.3%
Sodium Chloride	3.6	59.3%
Sorbitol	3.0	50.7%
Sucrose	1.3	21.4%

[0036] This test shows that the sugars used in the test have an ability to decrease the extent of preservative binding for of cationic preservatives when properly formulated. Both sorbitol and sucrose solutions demonstrated efficacy in reducing preservative deposition.

Example 6

[0037] The following experiment demonstrates the effect of chloride concentration on the antimicrobial effectiveness of PHMB preservative solutions.

Log

Reduction	Buffer	Preservative	NaCl	Additive	Effect
1.05	Bis-Tris 0.2%	PHMB 0.0001%	None	none	54%
1.47	Bis-Tris 0.2%	PHMB 0.0001%	None	None	75%
0.77	Bis-Tris 0.2%	PHMB 0.0001%	0.70%	None	39%
2.36	Bis-Tris Propane 0.2%	PHMB 0.0001%	None	None	123%
2.32	Bis-Tris Propane 0.2%	PHMB 0.0001%	None	None	119%
0.91	Bis-Tris Propane 0.2%	PHMB 0.0001%	0.70%	None	47%
1.27	Tricine 0.2%	PHMB 0.0001%	None	None	65%
1.31	Tricine 0.2%	PHMB 0.0001%	None	None	67%
0.62	Tricine 0.2%	PHMB 0.0001%	0.70%	none	32%

What is claimed is:

1. An ophthalmic solution comprising 0.00001 up to 0.001 weight percent of a simple saccharide chosen from the group consisting of: inositol; mannitol; sorbitol; ribose; triose; tetrose; erythrose; threose; pentose; arabinose; ribulose; xylose; xylulose; lyxose; hexose; allose; altrose; fructose; sucrose; dextrose; galactose; glucose; gulose; idose; mannose; sorbose; talose; tagatose; adlose; ketose; heptose; sedoheptulose; glycerin; xylitol; and polyol, at least 0.00001 weight percent of a preservative, and not more than about 0.2 percent by weight chloride; wherein said solution is effective as a single component solution.

2. The ophthalmic solution of claim 1 wherein the simple saccharide is inositol.

3. The ophthalmic solution of claim 1 wherein the simple saccharide is xylitol.

4. The ophthalmic solution of claim 1 wherein said preservative is polyhexamethylene biguanide with a concentration between 0.1 and 100 parts per million.

5. The ophthalmic solution of claim 1, wherein the concentration of said preservative is between 0.1 and 100 parts per million.

6. The ophthalmic solution of claim 1, further comprising a physiologically compatible buffer.

7. The ophthalmic solution of claim 6, wherein said physiologically compatible buffer is selected from the group consisting of: phosphate, bicarbonate, citrate, borate, ACES, acetate, BES, BICINE, BIS, BIS-Tris, BIS-Tris Propane, bicarbonate, histidine, HEPES, Tris, HEPPS, imidazole, MES, MOPS, PIPES, TAPS, TES, glycine, tromethamine, and Tricine.

8. The ophthalmic solution of claim 1, further comprising a wetting agent.

9. The ophthalmic solution of claim 8 wherein said wetting agent is selected from the group consisting of: polysorbate surfactants, polyoxyethylene surfactants, polyethoxylated glycerides, phosphonates, saponins and polyethoxylated castor oils.

10. The ophthalmic solution of claim 1 further comprising a sequestering agent.

11. The ophthalmic solution of claim 10 wherein said sequestering agent is selected from the group consisting of: ethylenediaminetetraacetic acid, phosphonates, citrate, gluconate, nitrilotriacetic acid, diethylenetriamine pentaacetic acid, hydroxyethylethylenediaminetriacetic acid, 1 ,2-diaminocyclohexanetetraacetic acid, ethylene glycol bis (beta-aminoethyl ether), tetraacetic acid (EGTA), aminodiacetic acid, hydroxyethylamino diacetic acid, tartarate, and water-soluble salts thereof.

12. An ophthalmic solution comprising 0.00001 up to 0.001 weight percent of a preservative enhancer chosen from the group consisting of: inositol; mannitol; sorbitol; sucrose; dextrose; glycerin; and propylene glycol; at least 0.00001 weight percent of a preservative; and not more than about 0.2 percent by weight chloride.

13. A contact lens solution comprising 0.00001 up to 0.001 weight percent of a simple saccharide chosen from the group consisting of: inositol; ribose; triose; tetrose; erythrose; threose; pentose; arabinose; ribulose; xylose; xylulose; lyxose; hexose; allose; altrose; fructose; galactose; glucose; gulose; idose; mannose; sorbose; talose; tagatose; adlose; ketose; heptose; sedoheptulose; xylitol; and polyol, at least 0.00001 weight percent of a preservative, and not more than about 0.2 percent by weight chloride, wherein said solution is effective as a single component solution.

14. An ophthalmic solution comprising 0.00001 to about 10.0 weight percent of a simple saccharide chosen from the group consisting of: ribose; triose; tetrose; erythrose; threose; pentose; arabinose; ribulose; xylose; xylulose; lyxose; hexose; allose; altrose; fructose; galactose; glucose; gulose; idose; mannose; sorbose; talose; tagatose; adlose; ketose; heptose; sedoheptulose; xylitol; and polyol, at least 0.00001 weight percent of a preservative, and not more than about 0.2 percent by weight chloride; wherein said solution is effective as a single component solution.

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(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 June 2008 (26.06.2008)

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WO 2008/077110 A3

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PCT/US2007/088167

(22) International Filing Date:
19 December 2007 (19.12.2007)

(25) Filing Language: English

(26) Publication Language: English

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11/613,029 19 December 2006 (19.12.2006) US

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Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
25 September 2008

WO 2008/077110 A3

(54) Title: OPHTHALMIC AND CONTACT LENS SOLUTIONS CONTAINING SIMPLE SACCHARIDES AS PRESERVATIVE ENHANCERS

(57) Abstract: The present invention relates to ophthalmic solutions comprising 0.00001 up to 0.001 weight percent of a simple saccharide, at least 0.00001 weight percent of a preservative, and not more than about 0.2 percent by weight chloride. The simple saccharide is chosen from the group consisting of: inositol, mannitol; sorbitol; sucrose; dextrose; glycerin; propylene glycol; ribose; triose; tetrose; erythrose; threose; pentose; arabinose; ribulose; xylose; xylulose; lyxose; hexose; allose; altrose; fructose; galactose; glucose; gulose; idose; mannose; sorbose; talose; tagatose; adlose; ketose; heptose; sedoheptulose; monosaccharides; disaccharides; sugar alcohols; xylitol; and polyol.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/088167

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61L12/14 A01N47/44 A01N33/12 C11D3/22 C11D3/37
C11D7/26 A61K9/00
ADD. A61L101/34 A61L101/44 A61L101/46
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61L A01N A61K C11D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/38161 A (BIO CONCEPT LAB [US]; SMITH FRANCIS XAVIER [US]) 16 May 2002 (2002-05-16) page 1, paragraph 1 page 2, line 1 - page 6, line 18; claims 1-7; examples 1,2,3A-F	1,2,4-13
A	US 6 617 291 B1 (SMITH FRANCIS X [US]) 9 September 2003 (2003-09-09) the whole document	1,2,4-13
A	WO 02/40062 A (BIO CONCEPT LAB [US]; SMITH FRANCIS XAVIER [US]) 23 May 2002 (2002-05-23) the whole document	1,2,4-13

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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 May 2008	01/08/2008

Name and mailing address of the ISA/	Authorized officer
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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/088167

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2004/091438 A (FXS VENTURES LLC [US]; SMITH FRANCIS X [US]; CRAWFORD KATHRYN S [US]) 28 October 2004 (2004-10-28) the whole document	1,2,4-13

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/088167

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

see annex

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1(part), 2, 4-11, 12(part), 13(part)

The first invention is directed to an ophthalmic or contact lens solution comprising 0.00001 to 0.001 wt.-% of inositol as polyol; at least 0.00001 wt.-% of a preservative, and not more than 0.2 wt.-% chloride

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2. claims: 1(part), 4-11, 12(part)

The second invention is directed to an ophthalmic solution comprising 0.00001 to 0.001 wt.-% of mannitol as polyol; at least 0.00001 wt.-% of a preservative, and not more than 0.2 wt-% chloride.

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3. claims: 1(part), 4-11, 12(part)

The third invention is directed to an ophthalmic solution comprising 0.00001 to 0.001 wt.-% of sorbitol as polyol; at least 0.00001 wt.-% of a preservative, and not more than 0.2 wt.-% chloride.

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4. claims: 1(part), 4-11, 13(part), 14(part)

The fourth invention is directed to an ophthalmic or contact lens solution comprising 0.00001 to 10.0 wt.-% of pentose as polyol; at least 0.00001 wt.-% of a preservative, and not more than 0.2 wt.-% chloride.
It is noted that the related alternatives of 0.00001 to 0.001 wt.-% pentose according to claims 1 and 13, the alternatives of 0.00001 to 10.0 wt.-% ribose, arabinose, ribulose, xylose, xylulose, lyxose according to claim 14, and the alternatives of 0.00001 to 0.001 wt.-% ribose, arabinose, ribulose, xylose, xylulose, lyxose according to claims 1 and 13 are dependent on the feature "0.00001 to 10.0 wt.-% pentose" according to claim 14.

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5. claims: 1(part), 4-11, 13(part), 14(part)

The fifth invention is directed to an ophthalmic or contact lens solution comprising 0.00001 to 10.0 wt.-% of triose as polyol; at least 0.00001 wt.-% of a preservative, and not more than 0.2 wt.-% chloride.
It is noted that the related alternatives of 0.00001 to 0.001 wt.-% triose according to claims 1 and 13 are dependent on claim 14.

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6. claims: 1(part), 4-11, 13(part), 14(part)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

The sixth invention is directed to an ophthalmic or contact lens solution comprising 0.00001 to 10.0 wt.-% tetrose as polyol; at least 0.00001 wt.-% of a preservative, and not more than 0.2 wt.% chloride.
It is noted that the related alternatives of 0.00001 to 0.001 wt.-% tetrose according to claims 1 and 13, the alternatives of 0.00001 to 10 wt.-% erythrose, threose according to claim 14, and the alternatives of 0.00001 to 0.001 erythrose, threose according to claims 1 and 13 are dependent on the feature "0.00001 to 10.0 wt.-% tetrose" according to claim 14.

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7. claims: 1(part), 4-11, 13(part), 14(part)

The seventh invention is directed to an ophthalmic or contact lens solution comprising 0.00001 to 10.0 wt.-% hexose as polyol; at least 0.00001 wt.-% of a preservative, and not more than 0.2 wt.-% chloride.
It is noted that the related alternatives of 0.00001 to 0.001 wt.-% hexose according to claims 1 and 13, the alternatives of 0.00001 to 10 wt.-% allose, altrose, fructose, galactose, glucose, gulose, idose, mannose, sorbose, talose, tagatose according to claim 14, and the alternatives of 0.00001 to 0.001 wt.-% allose, altrose, fructose, glucose (dextrose), galactose, gulose, idose, mannose, sorbose, talose, tagatose according to claims 1 and 13 are dependent on the feature "0.00001 to 10 wt.-% hexose" according to claim 14.

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8. claims: 1(part), 4-11, 12(part)

The eighth invention is directed to an ophthalmic solution comprising 0.00001 to 0.001 wt.-% sucrose as polyol; at least 0.00001 wt.-% of a preservative, and not more than 0.2 wt.% chloride.

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9. claims: 1(part), 4-11, 13(part), 14(part)

The ninth invention is directed to an ophthalmic or contact lens solution comprising 0.00001 to 10.0 wt.-% aldose as polyol; at least 0.00001 wt.-% of a preservative, and not more than 0.2 wt.-% chloride.
It is noted that the related alternatives of claims 1 and 13 are dependent on claim 14.

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10. claims: 1(part), 4-11, 13(part), 14(part)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

The tenth invention is directed to an ophthalmic or contact lens solution comprising 0.00001 to 10.0 wt.-% ketose as polyol; at least 0.00001 wt.-% of a preservative, and not more than 0.2 wt.% chloride.
It is noted that the related alternatives of claims 1 and 13 are dependent on claim 14.

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11. claims: 1(part), 4-11, 13(part), 14(part)

The eleventh invention is directed to an ophthalmic or contact lens solution comprising 0.00001 to 10.0 wt.-% heptose as polyol; at least 0.00001 wt.-% of a preservative, and not more than 0.2 wt.% chloride.
It is noted that the related alternatives of 0.00001 to 0.001 wt.-% heptose according to claims 1 and 13, the alternative of 0.00001 to 10 wt.-% sedoheptulose according to claim 14, and the alternative of 0.00001 to 0.001 wt.-% sedoheptulose according to claims 1 and 13 are dependent on the feature "0.00001 to 10.0 wt.-% heptose" according to claim 14.

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12. claims: 1(part), 3-11, 13(part), 14(part)

The twelfth invention is directed to an ophthalmic or contact lens solution comprising 0.00001 to 10.0 wt.-% xylitol as polyol; at least 0.00001 wt.-% of a preservative, and not more than 0.2 wt.-% chloride.
It is noted that the related alternatives of claims 1 and 13 are dependent on claim 14.

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13. claims: 1(part), 4-11, 12(part)

The thirteenth invention is directed to an ophthalmic solution comprising 0.00001 to 0.001 wt.-% glycerin as polyol; at least 0.00001 wt.-% of a preservative, and not more than 0.2 wt.-% chloride.

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14. claim: 12(part)

The fourteenth invention is directed to an ophthalmic solution comprising 0.00001 to 0.001 wt.-% propylene glycol as polyol; at least 0.00001 wt.-% of a preservative, and not more than 0.2 wt.-% chloride.

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15. claims: 1(part), 4-11, 13(part), 14(part)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

The fifteenth invention is directed to an ophthalmic or contact lens solution comprising 0.00001 to 10.0 wt.-% of polyol not covered by any of the preceding inventions 1 to 14; at least 0.00001 wt.-% of a preservative, and not more than 0.2 wt.-% chloride.
It is noted that the related alternatives of 0.00001 to 0.001 wt.-% "other polyol" according to claims 1 and 13 are dependent on claim 14.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2007/088167

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0238161 A	16-05-2002	AU 2720602 A	21-05-2002
		AU 2002227206 B2	21-09-2006
		CA 2428985 A1	16-05-2002
		CN 1486188 A	31-03-2004
		EP 1339418 A1	03-09-2003
		JP 4084997 B2	30-04-2008
		JP 2004512904 T	30-04-2004
US 6617291 B1	09-09-2003	NONE	
WO 0240062 A	23-05-2002	AU 2595002 A	21-05-2002
		AU 3954502 A	27-05-2002
		AU 2002225950 B2	10-08-2006
		AU 2002239545 B2	05-10-2006
		AU 2002251685 B2	27-10-2005
		CA 2428994 A1	15-08-2002
		CA 2428997 A1	23-05-2002
		CA 2434961 A1	16-05-2002
		CN 1486186 A	31-03-2004
		CN 1505520 A	16-06-2004
		CN 1486187 A	31-03-2004
		EP 1337262 A2	27-08-2003
		EP 1339414 A2	03-09-2003
		EP 1331902 A2	06-08-2003
		JP 2004512901 T	30-04-2004
		JP 2004525865 T	26-08-2004
		JP 2004526186 T	26-08-2004
		WO 0238077 A2	16-05-2002
		WO 02062260 A2	15-08-2002
WO 2004091438 A	28-10-2004	US 2008167246 A1	10-07-2008